Aus der Universitäts-Kinderklinik Basel (Direktor: Prof. A. Hottinger)

Polycythemia in an Eleven-Year-Old Girl

Inaugural-Dissertation
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Objective

The objective of this paper is to present a *case of polycythemia vera in a child*. According to WINTROBE (75) polycythemia vera is a disease of late middle age and very seldom occurs in children. In some of the cases which have been reported, there is insufficient evidence to rule out all secondary causes of polycythemia. Other than the interest compounded by the paucity of cases, our patient is to our knowledge one of the youngest diagnosed cases of primary polycythemia vera.

Introduction

Polycythemia was first described in 1892 by VAQUEZ (69). In 1902 TÜRK (68) added to the clinical picture leucocytosis with evidence of immature forms of both erythrocytic and leucocytic series being present. Thus suggesting to future clinicians VAUGHAN 1936 (77) and DAMESHEK 1951 (20) the possibility of an underlying myeloproliferative disorder. Then, OSLER in a monumental work clearly defined this syndrome as a specific disease entity. WINTROBE and GURNEY are of the opinion that comprehension of polycythemia vera at its present level can be acquired with OSLER and LAWRENCE (53) as a foundation and the assistance of a good review of the current work of investigators (33).

Case Report

Veronika B., a 14-year-old Caucasian girl, born 1953 in Hottingen, Germany (800 m over sea level), was admitted to the University's Children's Hospital in Basel with the chief complaint of complications in an established case of polycythemia vera. The patient was born at term, of a normal pregnancy and delivery. At birth she was 3.7 kg and 56 cm in length. Growth and development were normal. She lifted her head at 3 months, and sat at 7 months. Dentition began at 7 months. She stood at 8 months, and walked at 16 months. At 16 months she began to talk.

Since birth the child has never been completely free of symptoms. The mother remembers the child being redder than the other children.

Veronika always suffered from headaches which were more severe in warm weather and recurring upper respiratory infections.

On April 13, 1955, at the age of 2, the patient was admitted to the hospital at Waldshut. Her diagnosis was asthma complicated by bronchial pneumonia. She appeared cyanotic and the physical findings were ronchi and rales over the right lung. There were no cardial murmurs. Her temperature on admission was 40.2°C. She had a hemoglobin of 92% (16 g = 100%), a red cell count of 6.6 million and a white count of 19 000. A chest X-ray revealed a wide hilus with increased pulmonary vascular markings. There were no pathological changes in position, size or form of heart. The patient was treated with achromycine, cedilanid and nor-adrenalin. She was dismissed from Waldshut Hospital on May 6, 1955.

During the next 6 years the child was plagued by frequent headaches and upper respiratory infections which both occurred with increasing frequency. Her plethoric complexion remained constant. The patient had, during this period, the normal childhood diseases and suffered no complications. She had pertussis at 2½, rubeola at 4½, rubella at 5, scarlet fever and chicken pox at 6. In February 1961 the existing condition was complicated with epistaxis and hemoptysis. At that time, in Veronika's school a few cases of tuberculosis were diagnosed. Her chest X-ray was not entirely normal. The child was then sent to a tubercular clinic at Friedensweiler, where a red cell count of 7.6 million and a hemoglobin of 21.4 g% were found. Her tuberculin test was negative. In February 1962 the patient was admitted to the University of Freiburg's Children's Hospital to determine the cause of the polycythemia. She was discharged in April 1962 and followed in the outpatient clinics. She was readmitted with a mild pyuria in July 1964. During these two admissions the diagnosis of polycythemia vera was established and it was agreed by the staff that there should be no specific treatment, because there had been no increase in the red cell count and the previous symptoms had not increased in severity.

If there should be an increase in the erythrocytic count and/or the symptoms became intolerable, they could be controlled by phlebotomy.

During the ensuing year there was little change in the child's condition. Then, in August, Veronika's headaches began to occur more frequently and she became dizzy, nauseous and she vomited. On two occasions she saw black before her eyes and once she fainted. Then her right hand became clumsy. The child found it difficult to write, then to hold the pencil. Her hand 'began to move by itself'. Due to greater distance to the University of Freiburg, the patient was sent to the University's Children's Hospital in Basel.

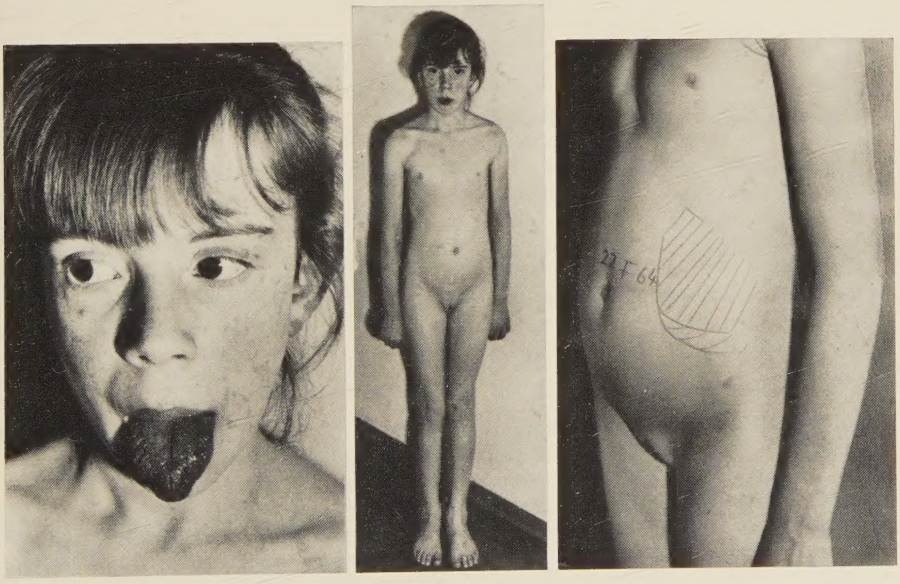
There the patient was seen for the first time by the author. Since then, the child has had three subsequent admissions for treatment of exacerbation of her symptoms. There is no evidence that any other

member of the patient's family had polycythemia vera. The maternal grandmother and grandfather are 75 and 95 years old, respectively. Both are in good health. The paternal grandmother has a mild allergic and asthmatic condition, otherwise is in good health. The paternal grandfather died at 81 of an esophageal carcinoma. Prior to the discovery of the neoplasm he was always in good health. The mother, three sisters and one brother all have allergic constitutions and mild cases of asthma. The mother was treated for anemia. The father and a brother have never been sick (Table I).

TABLE I

Family hematological findings

Patient		Birth	Test Date	RBC	Hb	WBC
1. Wilhelm:	father	1929	1962	4 mill.	14.5 g%	
2. Rita:	mother	1933	1960	3.88 mill.	13.2 g%	8600
3. Rudolf:	brother	1954	1962	4.73 mill.	13 g%	
4. Marianne:	sister	1957	1965	5 mill.	11.9 g%	6150
5. Waltraut:	sister	1959	1962	4.27 mill.	14.2 g%	9200
6. Reinhard:	brother	1961	1962	4.37 mill.	13 g%	
7. Andrea:	sister	1964	1966	4.73 mill.	13 g%	



Veronika B., 7. July 1964.

Physical examination revealed a slender female child with an accentuated plethoric complexion. She was alert, pleasant and cooperative. Her weight was 39.4 kg and her height was 154 cm.

Her cheeks, ears, hands and feet were a conspicuous ruddy red. Her lips, tongue and mucous membranes were a deep bluish red. The conjunctivae were slightly injected, otherwise eyes and ears were without pathological findings. There was a slight retromandibular lymphadenopathy.

The heart was not enlarged. There was a normal sinus rhythm of 70 per minute. The second sound over Erb's point was slightly accentuated. There were no murmurs. Her blood pressure was 110/90.

The lungs were clear to auscultation and percussion. The bilateral dorsal excursion of the lungs was one finger breadth and the respiratory rate was 22 per minute. The abdomen was soft and painless. The spleen was palpable three finger breadths below the left costal arch. The liver was also palpable. The neuromuscular status: the right hand was in an abnormal flexor position. The diadochokinesis of the right hand was mildly reduced. There were involuntary choreatic movements of the right hand, and the strength of the entire right arm was reduced. There was a mild apraxia in the right leg by one leg standing.

Laboratory Values

Hematological Values:

TABLE II

Pertinent Blood Data

Location	Age	Hb	RBC	Hct.	WBC	Platelets	Ret.
1. Waldshut, Germany	2	92 % (100% = 16 g)	6.6 mill.	—	19 000	—	—
2. Friedensweiler	8	21.4 g%	7.6 mill.	—	9 600	—	—
3. Freiburg, Germany	9	21.6 g%	9.15 mill.	80%	9 000	180 000	14%
4. Freiburg, Germany	11	22 g%	8.3 mill.	80%	6 000	51 000	14%
5. Basel, Switzerl.	12	19.4 g%	9.38 mill.	76%	5 800	120 000	16%
6. Basel, Switzerl.	13	14 g%	7 mill.	51%	9 700	185 000	49%
The change in hemoglobin and red cells is due to phlebotomy treatment at the previous admissions.							
7. Basel, Switzerl.	13	12 g%	7.06 mill.	50%	13 000	275 000	51%

Erythrocyte sedimentation rate:	0/0 mm/h
Total blood volume:	2350 ml = 96.3 ml/kg body weight
Plasma volume:	450 ml = 18.3 ml/kg body weight
Red cell volume:	1900 ml = 78 ml/kg body weight (method with Cr^{51} done at the University of Freiburg)
Plasma iron turnover:	(by the previous plasma volume and a serum iron = 21 y%) 0.14 mg Fe/h/liter full blood (method with Fe^{59} done at the University of Freiburg)

Bone marrow: the aspect was hypercellular.

pronormoblast	0.0
makronormoblast	1.0
basophil normoblast	16.0
polychrom. normoblast	31.5
oxyphile normoblast I	4.0
oxyphile normoblast II	2.5
	55.0/100

There were no pathological changes in the different developmental stages.

1. *Neutrophil*

neutrophiloblast	0.0
n. promyelocytes	3.0
n. myelocytes	9.0
n. metamyelocytes	7.5
n. band nucleus	23.5
n. segment nucleus	23.5

2. *Eosinophil*

e. band nucleus	2
e. segment nucleus	2

3. *Monocytes*

promonocytes	1.5
monocytes	2.0

4. *Basophil*

basophil	0.0

5. *Lymphocytes*

lymphocytes	21.0

6. *Megakaryiocytes and platelets*

megakaryoblasts	are present
promegakaryocytes	are present
megakaryocytes	are present
platelets	are present

Price Jones curve: normal
Osmotic resistence of red cell: normal
Mean corpuscular volume: 78 μ^3
Mean corpuscular hemoglobin: 24 $\gamma\gamma$
Methemoglobin, sulfhemoglobin: negative

Coagulation analysis:

	(normal)		(after heparin)
Quick	(70–100%)	41%	76%
coagulation time	(6–11′)	19′	
recalcification time	(60–120″)	140″	
fibrinogen	(200–500 mg%)	200 mg%	210 mg%
prothrombin	(70–100%)	47%	82%
factor V	(70–100%)	21%	86%
factor VII	(70–100%)	52%	72%
factor X	(70–100%)	60%	54%

bleeding time	(2–6′)	$11^1/_2'$
retraction	(100%)	20%
Rumpel-Leede		neg.
euglobulinlyse time	(2–6 h)	2 h
platelets	(200 000)	172 000

Most factors were decreased. There was in spite of it no proof for intravascular coagulatra: the fibrinogen was normal, as was the platelet count and the euglobulinlyse.

Serum Values:

Serum cu.:	250 mg%
Serum fe.:	41 y%
Serum na.	139 mg/100 ml
Serum k.	4.6 mg/100 ml
Serum ca.	4.7 mg/100 ml
Serum proteins:	total proteins 7.3 g%

Electrophoretic analysis:	albumin	52%
	globulin	48%
	$alpha_1$	6%
	$alpha_2$	8%
	beta	13%
	gamma	21%

Liver Function Tests:

SGOT:	85 U
SGPT:	32 U
BSP:	normal
Thymol turbidity:	+
Bilirubin:	1.39 mg%
Galactose tolerance:	normal

X-Rays:

Chest:	hili are enlarged. There are increased vascular markings. The right atrium is accentuated.
Skull:	no pathological findings. The sella is well defined and the Pineal Body is in the middle.
Abdominal:	no pathological findings. Renal shadows appear normal.
I.v. pyelogram:	after 4 minutes good excretion both sides with no deformities of the renal calyces or pelvis. There were no pathological changes in the renal shadows. There was nothing to suggest a tumor.

Pulmonary Tests:

1. *Pulmonary volumes*

Vital capacity:	2230 ml
Inspiratory reserve volume:	1378 ml
Expiratory reserve volume:	–
Functional residual capacity:	704 ml
Residual volume:	1825 ml
Total lung capacity	3203 ml

2. *Pulmonary functions:*

One-sec. timed vital capacity:	77.5%
Three-sec. timed vital capacity:	100%
Maximum breathing capacity (lit./min. ATPS):	250
Resting ventilation (lit./min. ATPS) by a breathing rate of 36	41.4

3. *Arterial blood oxygen saturation:* 100%

Renal Tests:

Urinanalysis:	within normal limits
Glomerular filtration rate:	123 ml/min/1.73 m^2
Renal plasma flow:	384.6 ml/min/1.73 m^2
Filtration fraction:	34.9% The results are normal for the high hematocrit.
Blood urea nitrogen:	36 mg%.
Electrocardiogram:	rate 70/min, rhythm normal sinus, heart vertical position, slight right side hypertrophy and conduction normal.
Electroencephalogram:	the activity over the right hemisphere is within normal limits. The activity over the left hemisphere is intermittently disturbed over the occipito-temporal areas (by hyperventilation also over the fronto-temporal area). There might be an organic base to the disturbance. A disturbance in the normal pattern is present. An EEG done a year earlier at the University of Freiburg was normal.
Lumbar Puncture:	Normal with a positive Queckenstedt.

Treatment and Course

During Veronika's first admission, October 1965, she received 5000 U of heparin intravenously and 20 000 U in an infusion over 24 hours. The coagulation factors, which were low on admission, showed a marked improvement. At this time it was decided to use phlebotomy. 1.7 liters of blood were removed over a period of five weeks until the hematocrit was 55% (55% was chosen, because the value according to WINTROBE was high enough to prevent increased erythropoietic activity and low enough to prevent possible complications of the disease). The patient was released in December 1965 and hematocrit, prothrombin time and reticulocytes were followed every two weeks in the out-patient clinics. A phlebotomy every 2 months was shown to be sufficient to maintain a hematocrit of 55%. Thus the patient was supported until her second hospital admission in March 1966. When she entered with symptoms similar, but milder (using her EEG and the disturbance in diadochokinesis of the right arm), to her previous admission, her hematocrit was 51%. She had an immediate phlebotomy, 300 ml were removed,

and she received 5000 U of heparin intravenously and 20 000 U over 24 hours in an infusion for three days. During this time the patient improved and at the end of three days the infusion was stopped. Then she had a slight relapse. Since there were no signs of cerebral bleeding (lumbar puncture was normal) and there were no changes in the coagulation factors, a heparin infusion of 15 000 U/day for 4 days was given and another phlebotomy of 290 ml was done. The patient was discharged on March 19, 1966. She was followed in the out-patient clinics as earlier described, except a hematocrit of 50% now was maintained. Again in December 1966 the patient entered the hospital. She had a right-sided hemiparese located chiefly in the right arm and more discreetly in the right leg. The EEG was interpreted to show a greater disturbance than on the two previous admissions. The red cell count was 7.06 million; the hemoglobin was 11.69%; the leucocytes were 13 000 with a shift to the left and a hematocrit of 50%. It was decided to anticoagulate the patient permanently with marcoumar. Due to the cell increase and the unfavorable viscosity a folic acid antagonist, Pyrimethamine (Daraprim) is being used intermittently. Since the discharge in January 1967, the patient is well and has suffered no relapses (June 1967). The hematological values are now held below 5.5 million/cmm erythrocytes and below a hematocrit of 50%.

Discussion

Because of the rarity of polycythemia vera in children, we thoroughly searched both through a complete physical examination and clinical tests for the possible existence of a cause of secondary polycythemia.

The differential diagnosis of polycythemia can be classified into primary polycythemia (polycythemia vera) and polycythemia from secondary causes. The latter can be subdivided into: (1) tumors (some have been proven and others are postulated to be bound to the polycythemia by an erythropoietic activating hormone), (2) any disease which causes a chronic reduction in the arterial blood oxygen saturation. Since the secondary causes are by far the most predominate, we began our investigation here.

Bronchopulmonary diseases such as emphysema, pulmonary fibrosis, a–v fistula, chronic cor pulmonale and cavernous hemangioma were excluded by: pulmonary tests which were well within the normal range, while the arterial blood oxygen saturation was 100%; chest X-rays with other than findings explained by hypervolemia were normal. Both cyanotic congenital and acquired heart diseases can be eliminated through the chest X-rays, the electrocardiogram, physical examination and the arterial blood oxygen saturation. A search for methemoglobin and sulfhemoglobin in the blood proved fruitless.

Many renal lesions both neoplasms such as hypernephroma, fibromyxoma and a benign adenoma; and non-neoplasms such as polycystic kidneys, hydronephrosis, bilateral renal cysts and unilateral renal cysts have occurred with polycythemia. Therefore, in order to eliminate the previous disorders as a possible cause, a thorough investigation of the kidneys was made. Both the abdominal X-ray and i.v. pyelogram exhibited no pathological findings: there were no deformities, no evidence of a tumor, and a good excretion on both sides. The glomerular filtration rate and renal plasma flow likewise were normal. A few carefully conducted urin analyses were within normal limits. Thus, the kidneys were excluded as a possible origin of the polycythemia (7, 14, 16, 22, 28, 29, 46, 54).

In recent years there has been a renewed recognition that an increased erythropoietic activity can accompany liver pathology such as cirrhosis, hepatocarcinoma, hamartoma and infectious hepatitis. The mechanism here is postulated to be the inability of the liver to inactivate the erythropoietin (43). With this in mind the liver functions were surveyed: the excretion function of the liver, using serum bilirubin and bromsulphalein tests as criterions, was normal; the synthesis function proved to be normal, using serum proteins with their electrophoretic analysis and thymol turbidity; the storage of carbohydrates tested by galactose tolerance was normal and both SGOT and SGPT were normal. No pathology could be located in the liver (5, 26, 47, 48).

A careful physical examination and an abdominal X-ray ruled out a uterine myoma; a cerebral angioma was eliminated as possible cause of the polycythemia by an electroencephalogram, skull X-ray, a lumbar puncture with a positive Queckenstedt and the absence of physical signs of increased cranial pressure (7, 12, 18, 37, 67, 72, 73).

After definitely removing the possibility of a secondary cause in our case of juvenile polycythemia vera, we returned our attention to primary polycythemia. Primary polycythemia is divided into a benign familial form and polycythemia vera. This classification was established by HOTTINGER (38). In the former there is a lack of symptoms (headaches, dizziness, fatigability, etc.), absence of both leucocytosis and thrombocytosis and the presence of a family history. After a careful search through Veronika's family, no evidence could be found that polycythemia had ever occurred.

Returning to the difference in polycythemia vera and benign familiar polycythemia there does not appear to be a clear division between the two entities if the differential criteria is applied. WINTROBE and SZUR both report that 25% of the cases of polycythemia can occur without both leucocytosis and thrombocytosis (66). In four out of five of polycythemia vera recorded in the English language in children none have leucocytosis or thrombocytosis, but they all have symptoms of the disease (Table III). In one case of benign familiar polycythemia there is no

TABLE III

Case	CROSATO	DAMON	MARLOW	HALBERTSMA	JAFFEE	
Family history	none	none	none	none	none	
Platelets	170 000	normal	640 000	—	120 000	A constant shift to the left is present with 10–25% neutrophil band nuclei
Leucocytes	4800	6200	11 900	5600	5800	
Hemoglobin	24.3 g%	20 g%	19.6 g%	21 g%	19.5 g%	
Body form	above average in height and below average in weight	no information available	tall and slender	tall and slender	tall and slender	
Age at diagnosis	11½	9½	9	6	10	
Symptoms	emesis headaches upper respirator infections, fainting	no symptoms	blurring of vision headaches nausea vomiting upper respiratory infections	blood shot eyes, headaches	headaches nausea emesis upper respiratory infections fainting neurological disturbances	
Illness in common	measles chicken-pocks pertussis gastro enteritis	measles	paratyphoid A. measles Chicken pocks tonsillitis	enteritis measles pertussis	measles chickenpocks pertussis scarlet fever	
Hematocrit	71.5%	70.4%	61%	-	76%	

family history and in another there is a trombocytic count of 324 000 (1). It could be possible that both entities are different degrees of the same disease.

A good survey of the earlier cases of familiar polycythemia can be found in NADLER and COHN and a more recent survey can be found in ABELDGAARD (1). It must be remembered that due to the lack of present-day sophisticated laboratory technics many of the reports of both types of primary polycythemia should be accepted with a certain degree of scepticism, if written before 1940.

Interestingly, the age of diagnosis could be lowered to two or assumed to have existed since birth. The child always suffered from the symptomatology of polycythemia vera (plethoric complexion, headaches and upper respiratory infections). At the age of two in Waldshut Hospital a confirmed red cell count of 6.6 million was made. A high erythrocytic count is one of the best indices of polycythemia vera (15). Shortly before the patient's admission to Friedenweiler she had hematemesis and hemoptysis which can also be included in the symptoms of the disease (45).

There are five cases of polycythemia vera in children recorded in the English language (21, 17, 34), one in Russian (13) and one from Czechoslovakia (10). They are compared in Table III.

Another interesting point is the possibility of our patient exhibiting signs of a cerebral thrombosis; without one being present a parallel can be seen in patients, suffering from polycythemia vera, who show typical signs of myocardial infarction in the ECG without one being found by the pathologists (9, 50, 65).

Summary

A case of polycythemia vera in an 10-year-old girl is presented with a short review of her therapy. Four other well documented cases are presented and a comparison of all are made. Some speculation on the difference between benign familiar polycythemia and polycythemia vera is done.

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